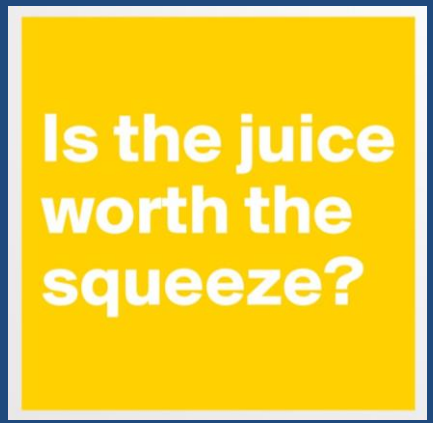
GI12
06/282020
11:13pm

Aatur Singhi, M.D., University of Pittsburgh Medical Center

UPMC LIFE CHANGING MEDICINE

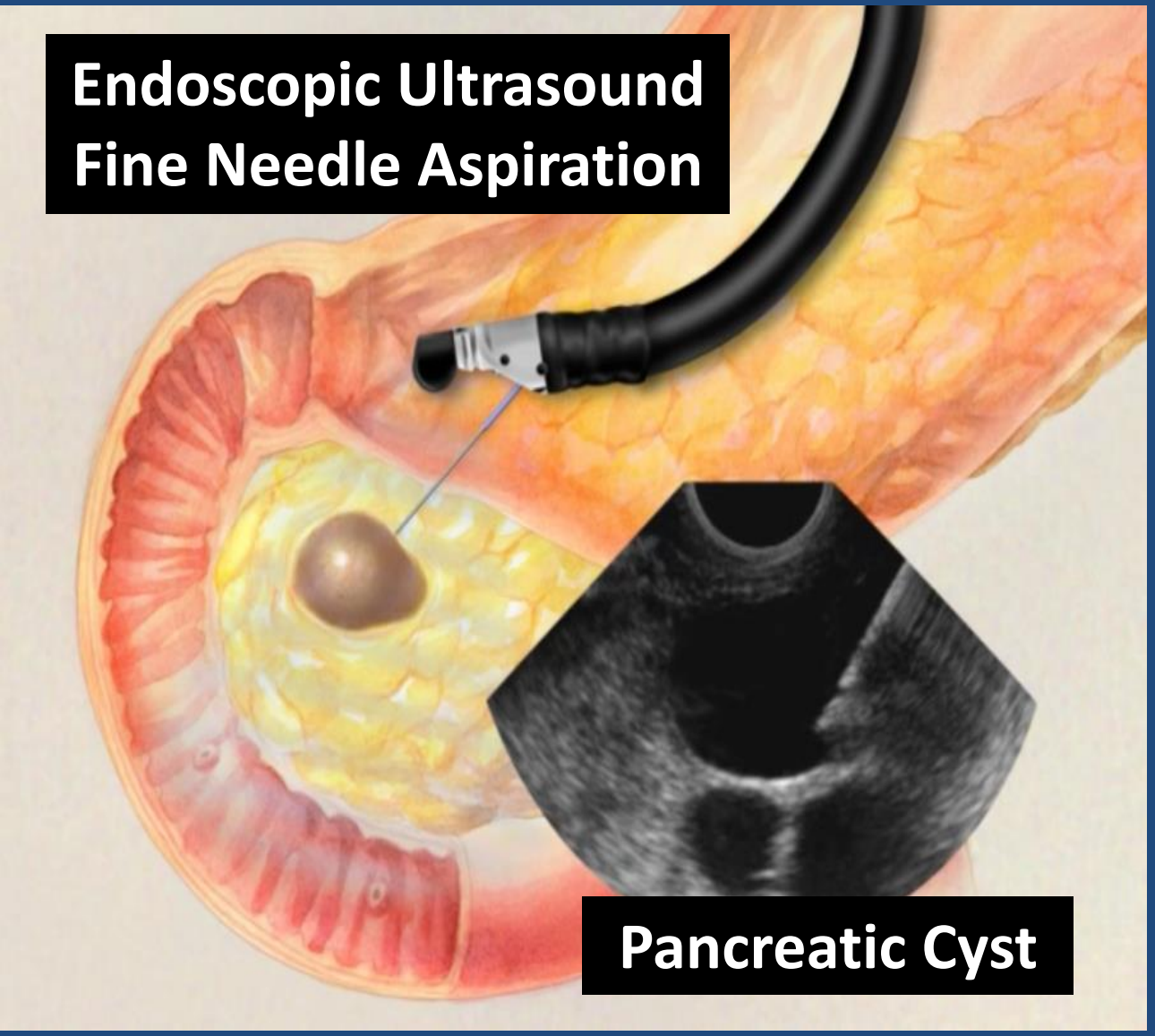
An Update to the Pancreatic Cyst Biomarker Alliance (PCBA): Is the (cyst) juice worth the squeeze?

Aatur D. Singhi, MD PhD
University of Pittsburgh Medical Center



56,770	Estimated new cases of pancreatic cancer (equivalent number of deaths).
8,515	Pancreatic cancers arising from a mucinous pancreatic cyst (IPMN/MCN).
6,462,000	Number of Americans with a **pancreatic cyst**.
3,231,000	Number of Americans with a **mucinous pancreatic cyst**.

Pancreatic Cysts



Adapted from Elyssa Siegal (Copyright 2011).

- **Endoscopic ultrasound (EUS) allows for high resolution imaging of the pancreatic cyst and relationship to the main pancreatic duct.**
- **Ancillary studies using aspirated cyst fluid include: CEA (marker of mucinous cysts), and cytopathology.**

Pancreatic Cysts Biomarkers

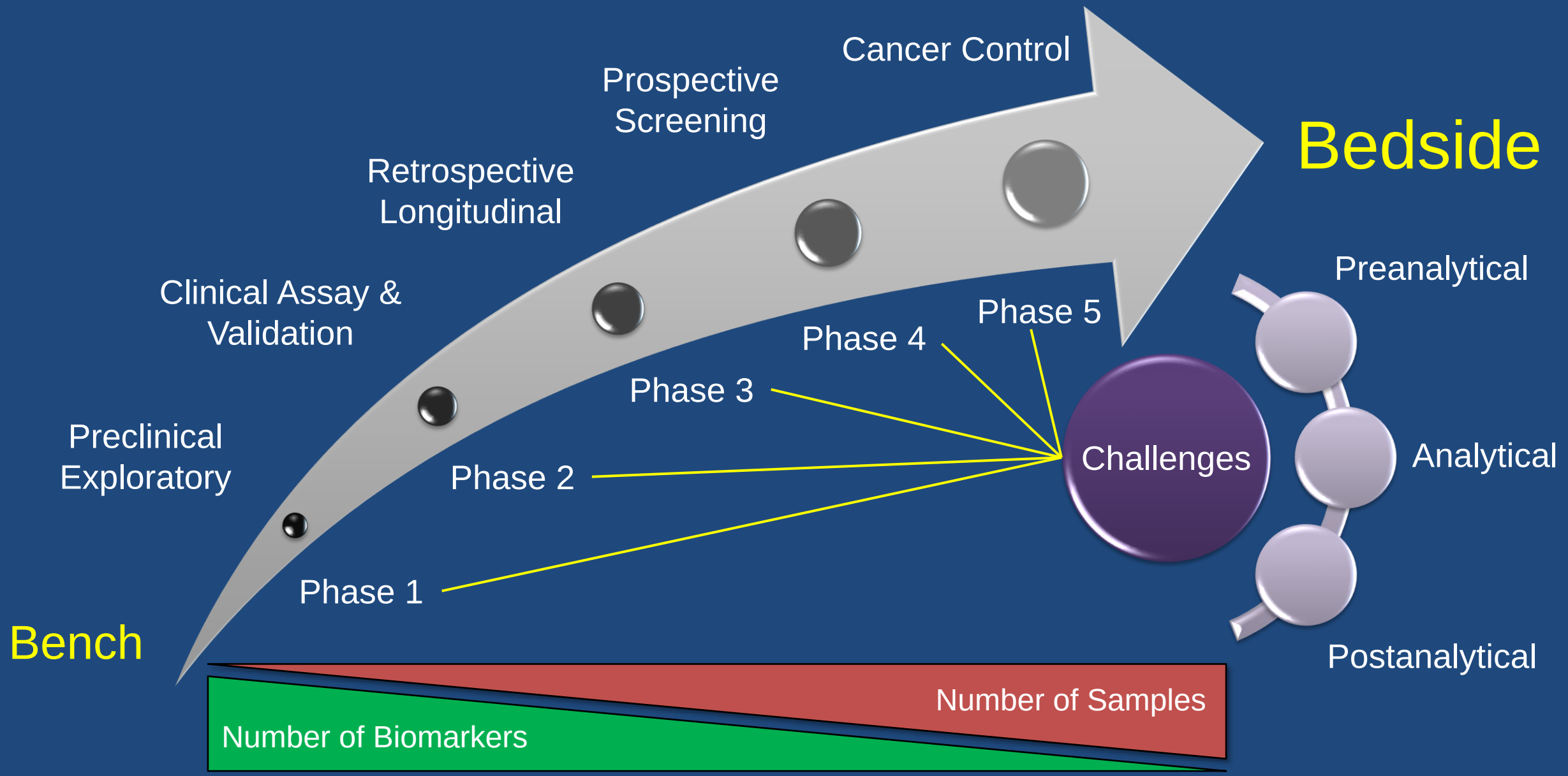
- Focus: Pancreatic Cyst Fluid
  - Integrated into standard clinical practice
  - Other specimens require further rigorous testing: serum, plasma, urine and stool

- Two sets of pancreatic cyst fluid biomarkers exist:
  - Mucinous (malignant potential) vs. non-mucinous cysts
  - Advanced neoplasia (malignancy) vs. not

Pancreatic Cysts Biomarkers

- Pancreatic Cyst Biomarker Alliance (PCBA)
- Demonstrate superiority to CEA
  - Sensitivity: 55-75%
  - Specificity: 70-84%
- Demonstrate superiority to current pancreatic cyst guidelines (e.g. Fukuoka guidelines)
  - Sensitivity: 35-55%
  - Specificity: 66-73%

Biomarker Development



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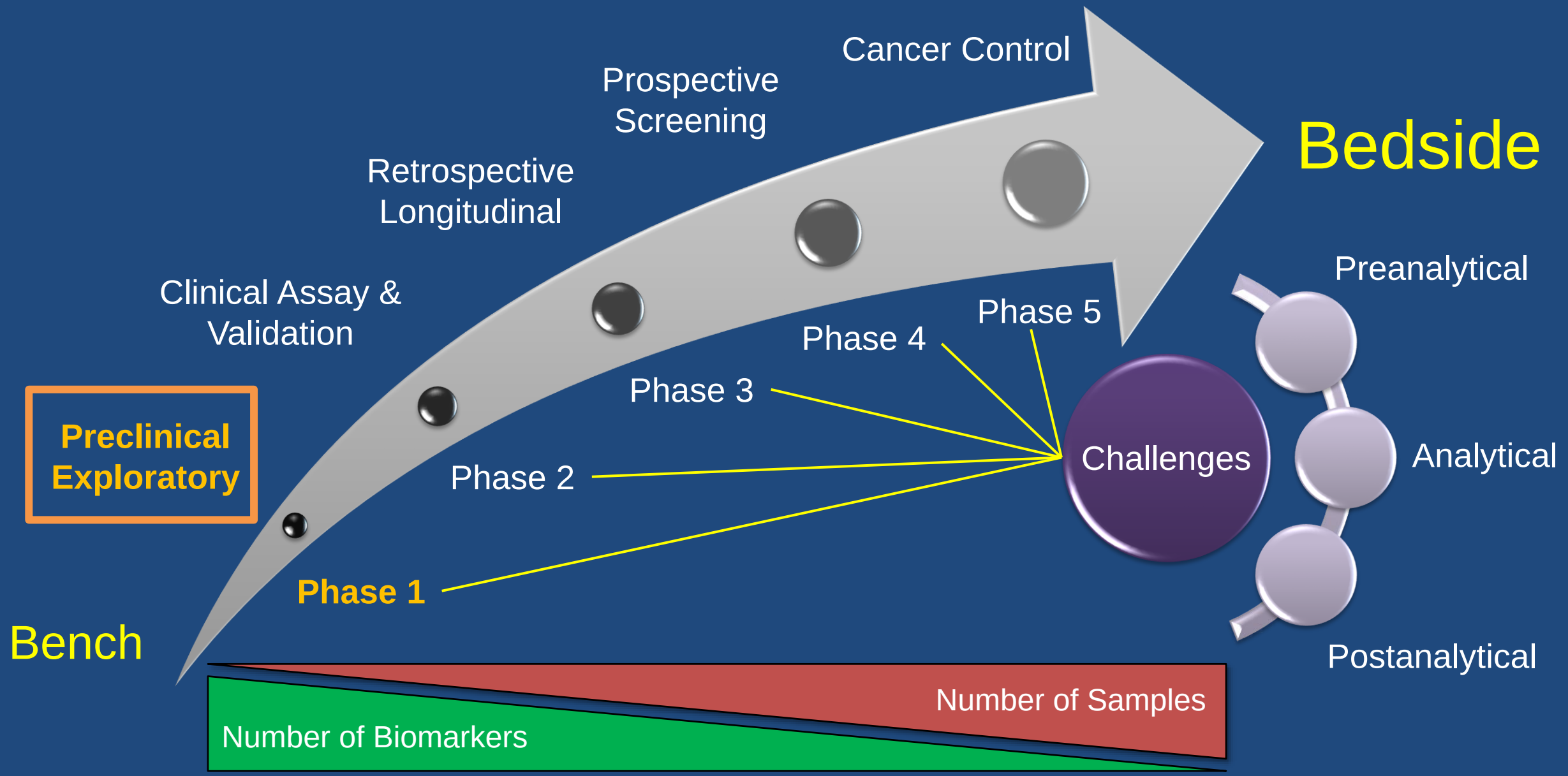
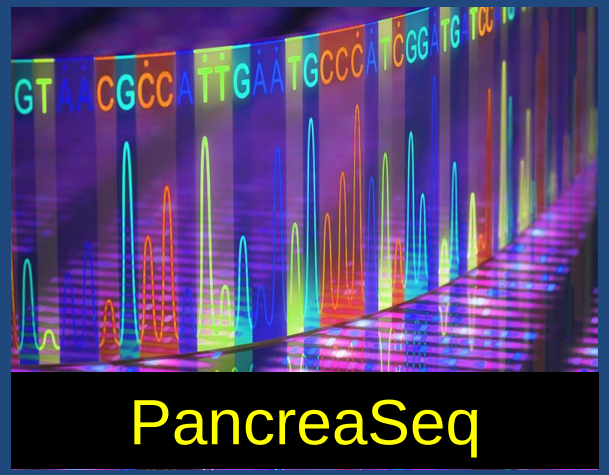
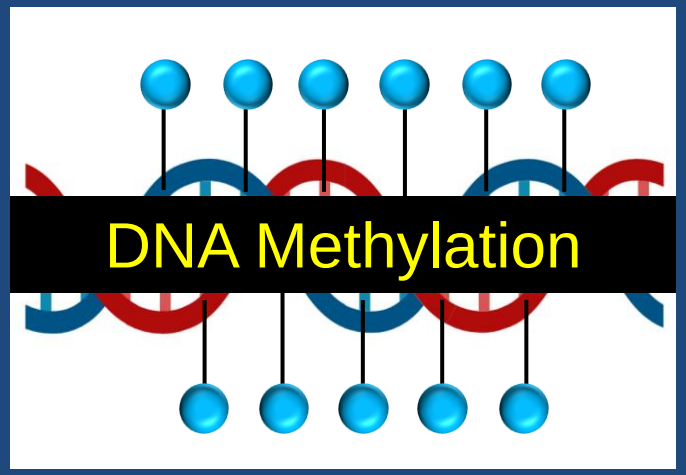
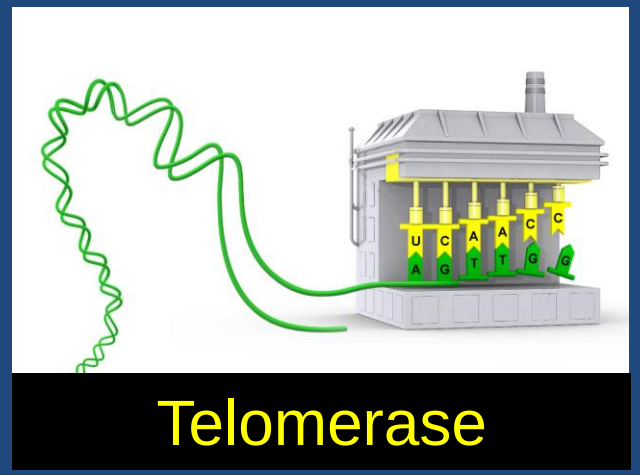
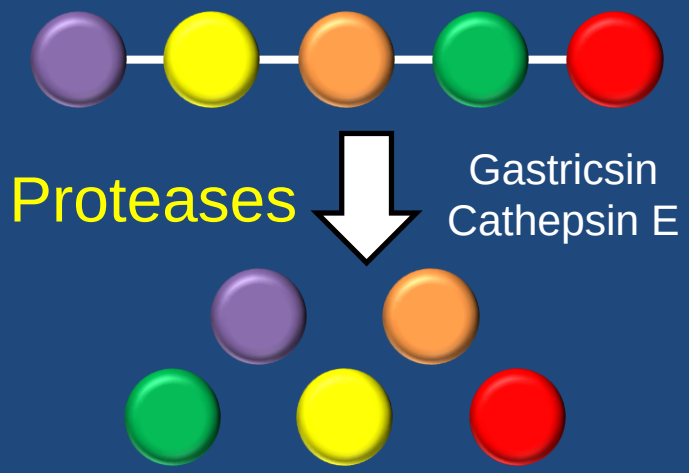


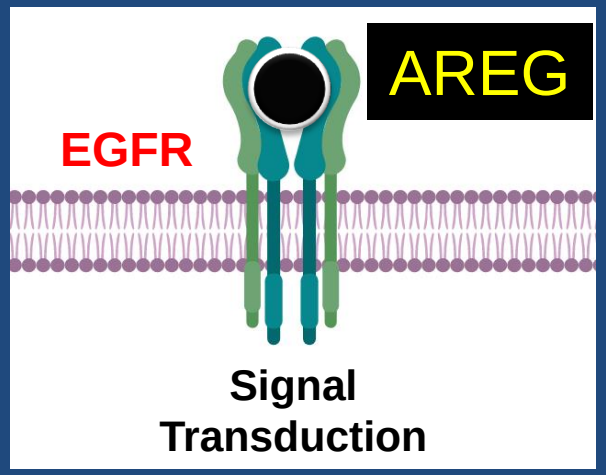
Pancreatic Cyst Fluid Biomarker Assays

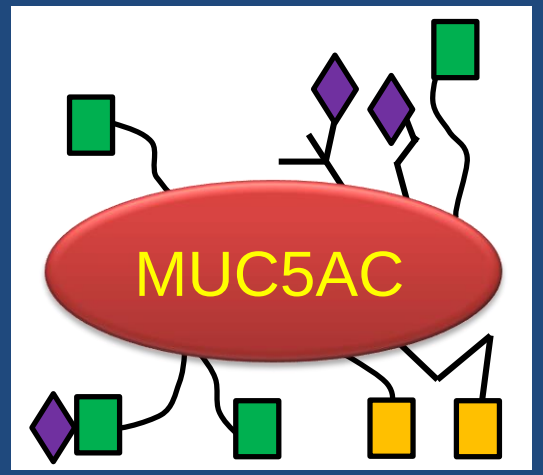












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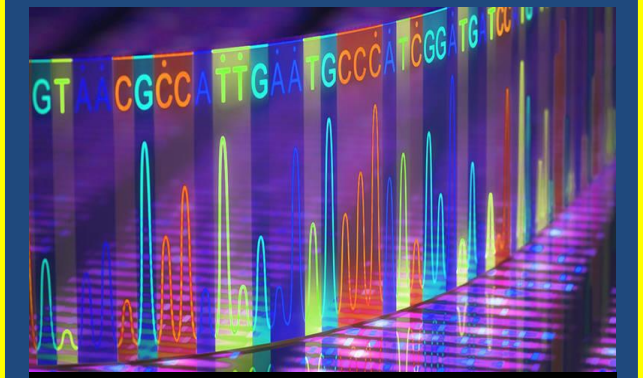
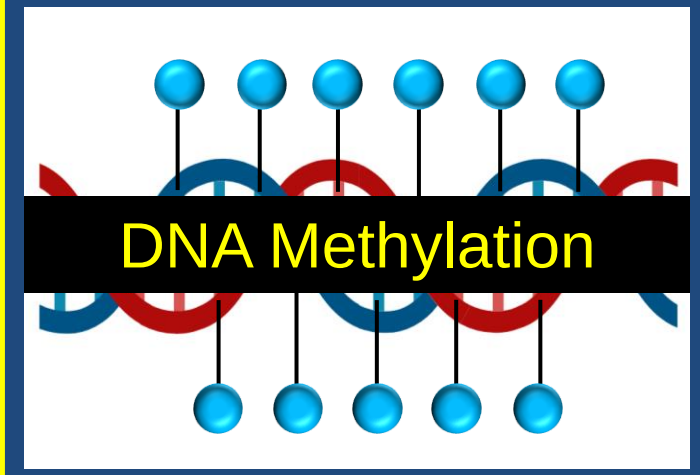
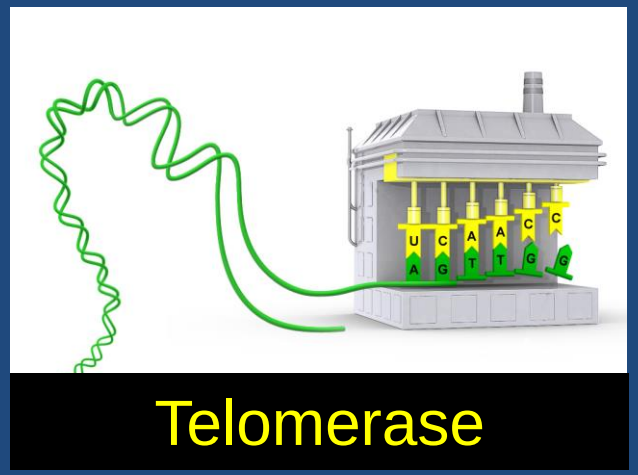


PancreaSeq

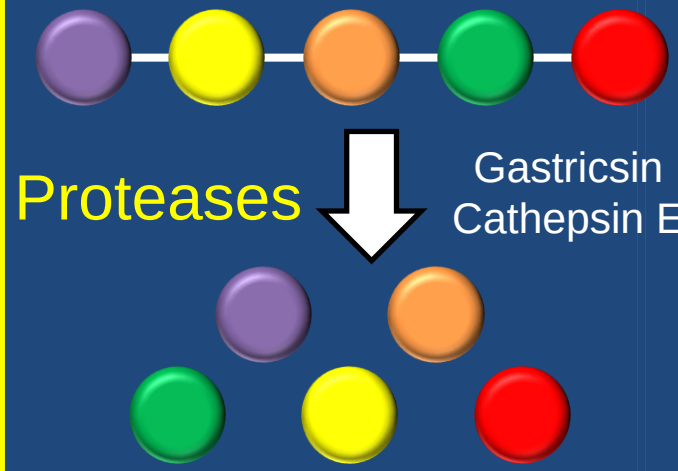


DNA Methylation



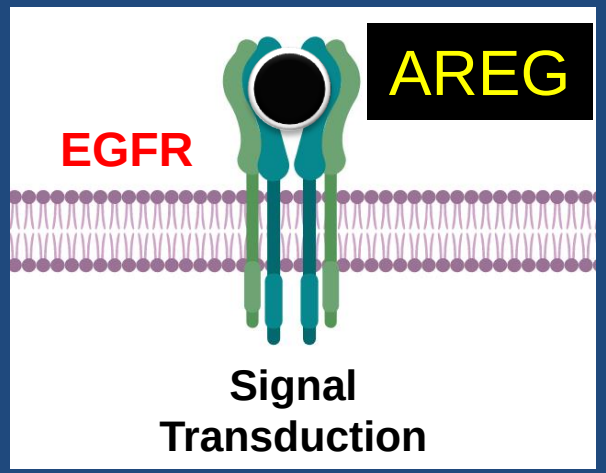
Telomerase

Das-1 Ab



Proteases

Gastricsin
Cathepsin E

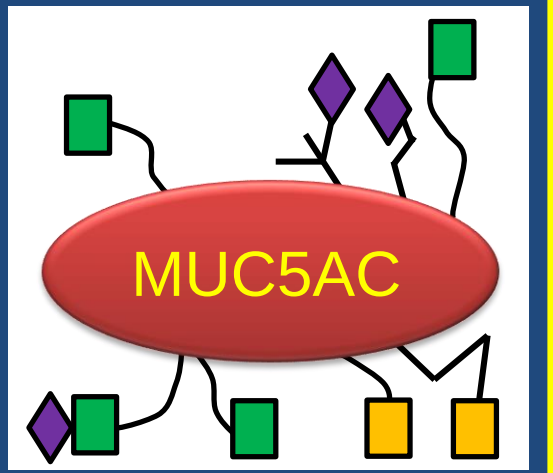


AREG

EGFR

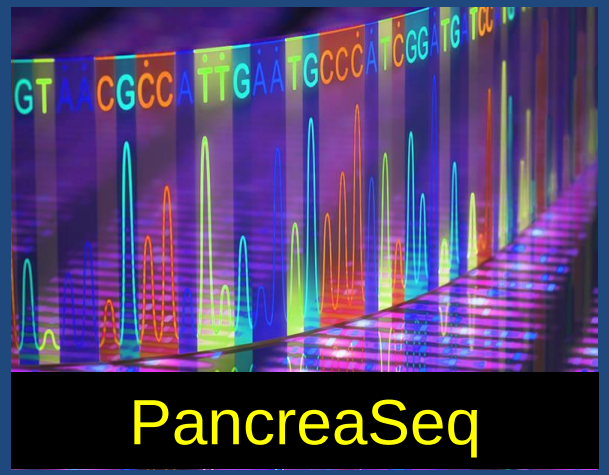
Signal
Transduction

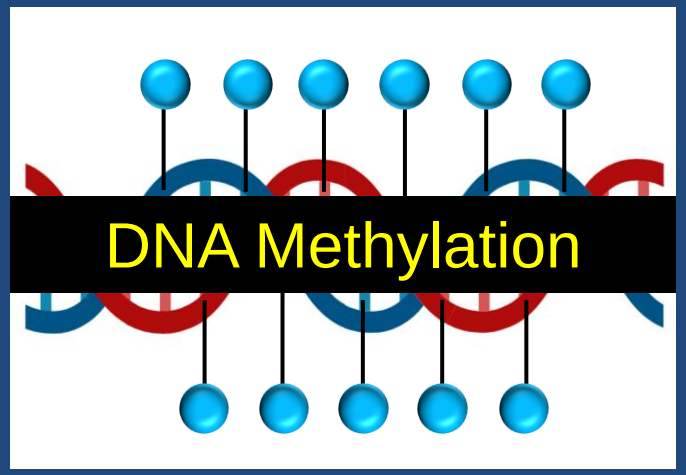
Glucose

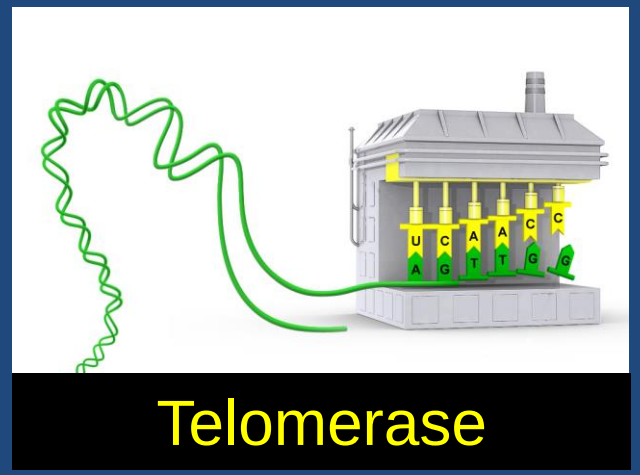


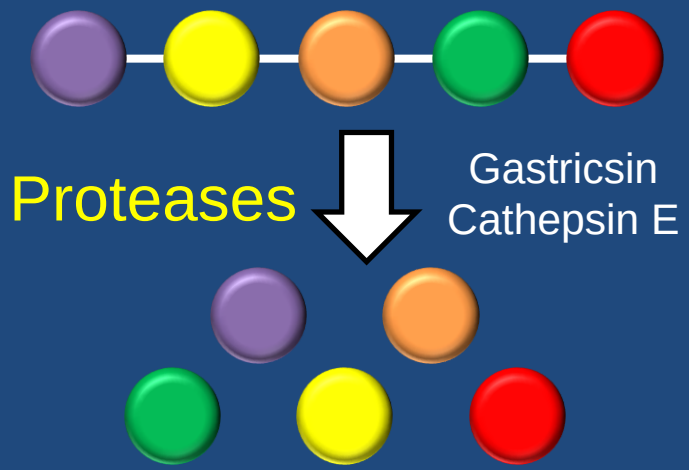
MUC5AC

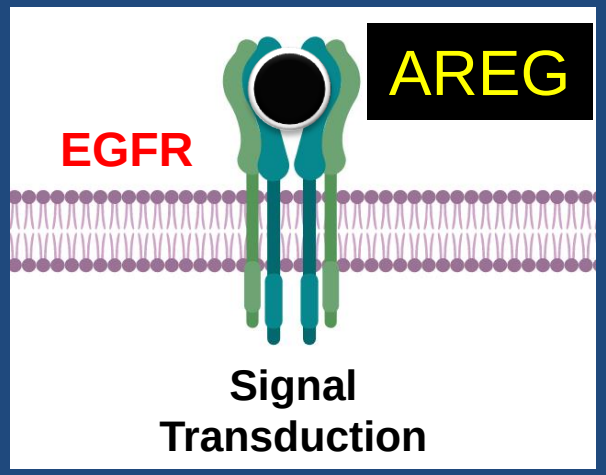
Pancreatic Cyst Fluid Biomarker Assays

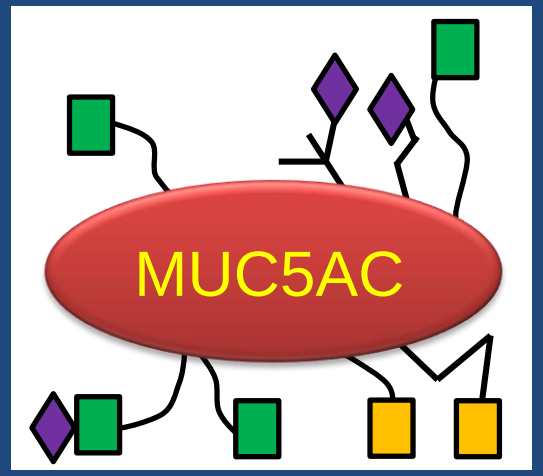




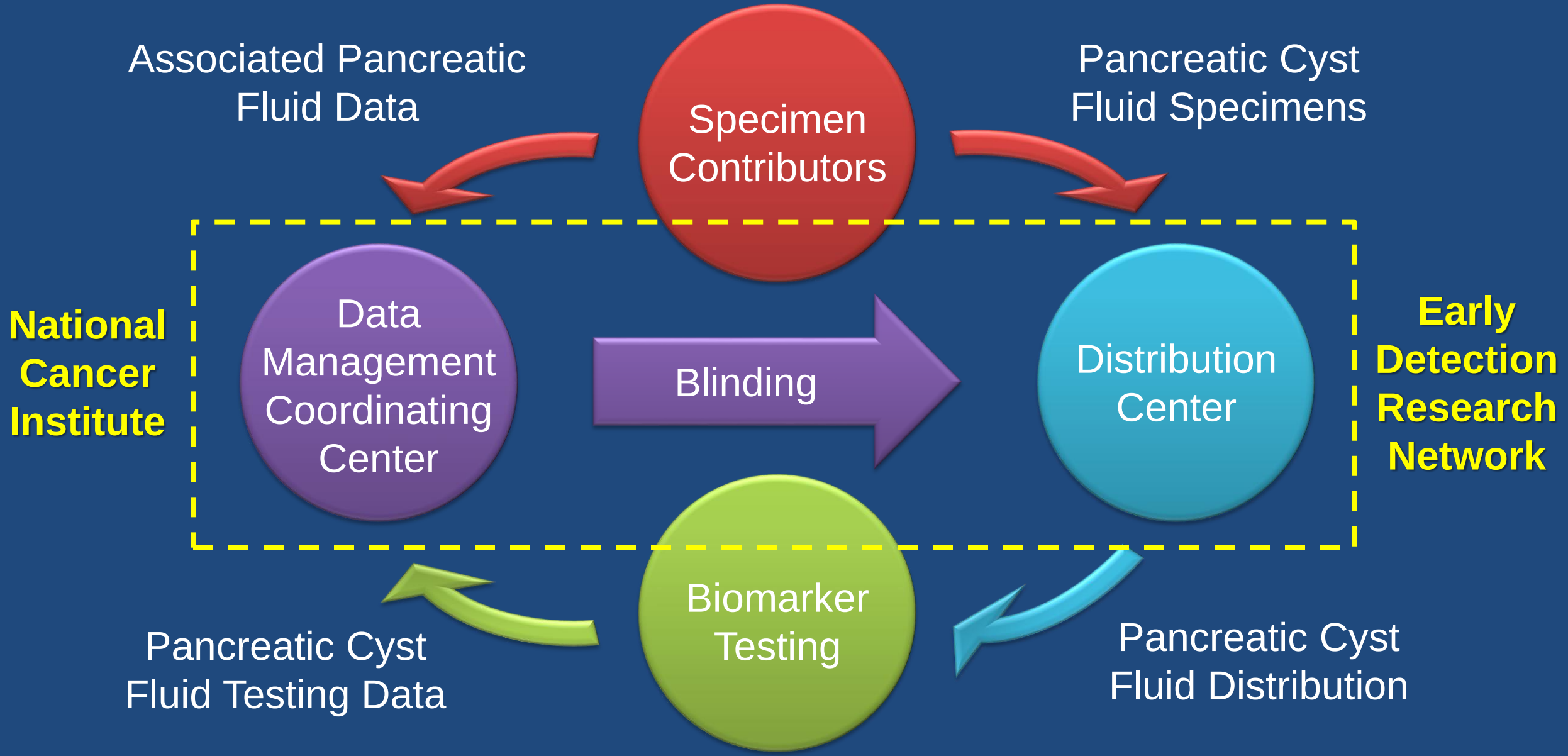








Pancreatic Cyst Biomarker Validation Study



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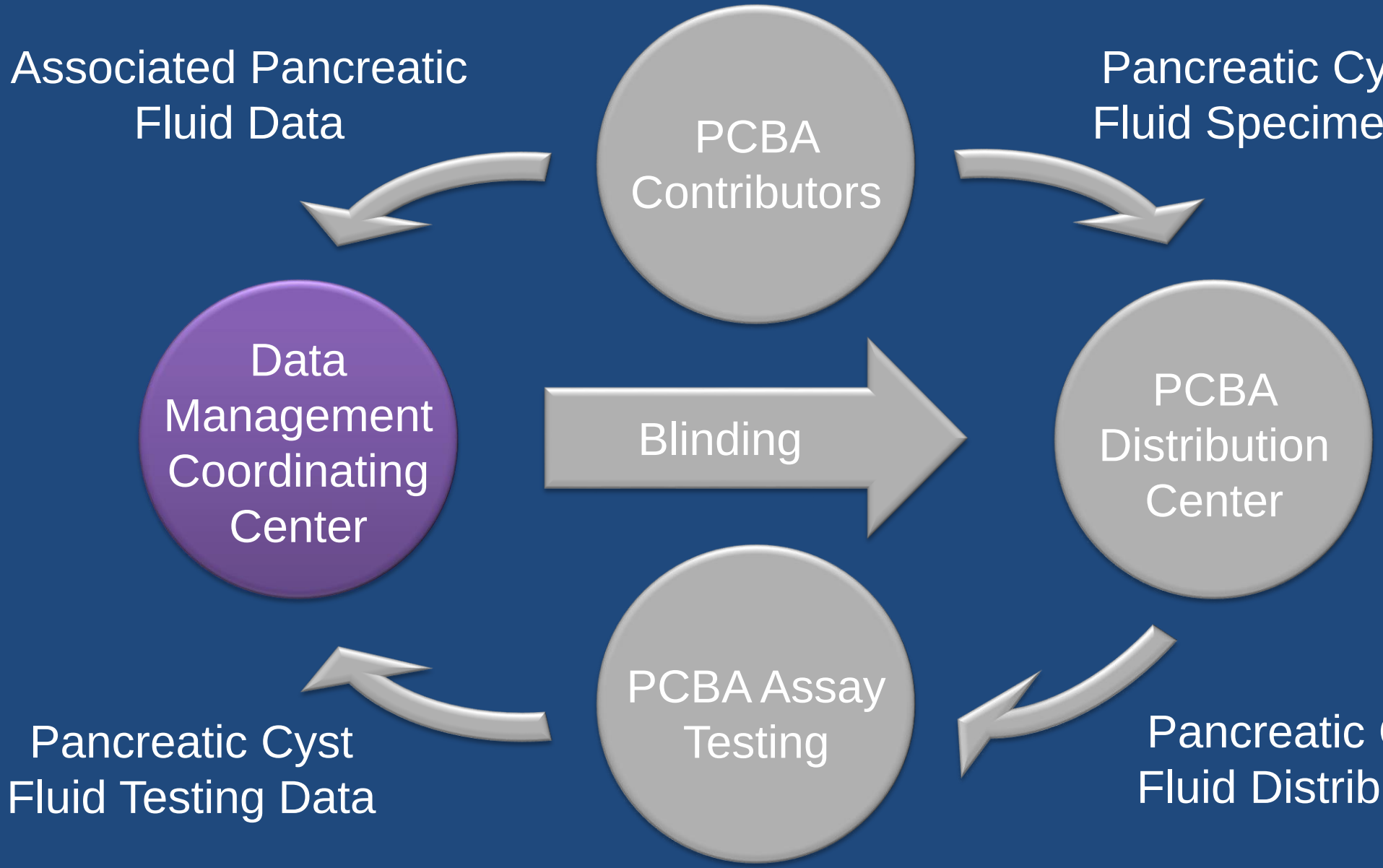

Pancreatic Cyst Biomarker Validation Study

Mucinous vs. Non-mucinous Cyst	Assay	Sensitivity	Specificity
	Proteases	72% (64% - 79%)	90% (83% - 96%)
	MUC3AC/MUC5AC	86% (80% - 92%)	70% (58% - 81%)
	AREG	65% (57% - 73%)	47% (36% - 59%)
	Glucose	90% (85% - 95%)	78% (67% - 88%)
	PancreaSeq	75% (69% - 82%)	100% (100% - 100%)

- The goal is to identify pancreatic cyst fluid biomarkers that demonstrate superiority to CEA
  - Sensitivity: **55-75%**
  - Specificity: **70-84%**

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Advanced Neoplasia vs. Not

Assay	Sensitivity*	Specificity
Assay 1	32% (19% - 45%)	81% (75% - 87%)
Assay 2	62% (49% - 75%)	92% (87% - 96%)
Assay 3	61% (48% - 75%)	87% (82% - 96%)
Assay 4	44% (31% - 58%)	92% (87% - 96%)

*Considering the low sensitivity of all assays, consensus pathologic evaluation is required and forthcoming.

Pancreatic Cyst Biomarker Validation Study

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  - Sensitivity: **35-55%**
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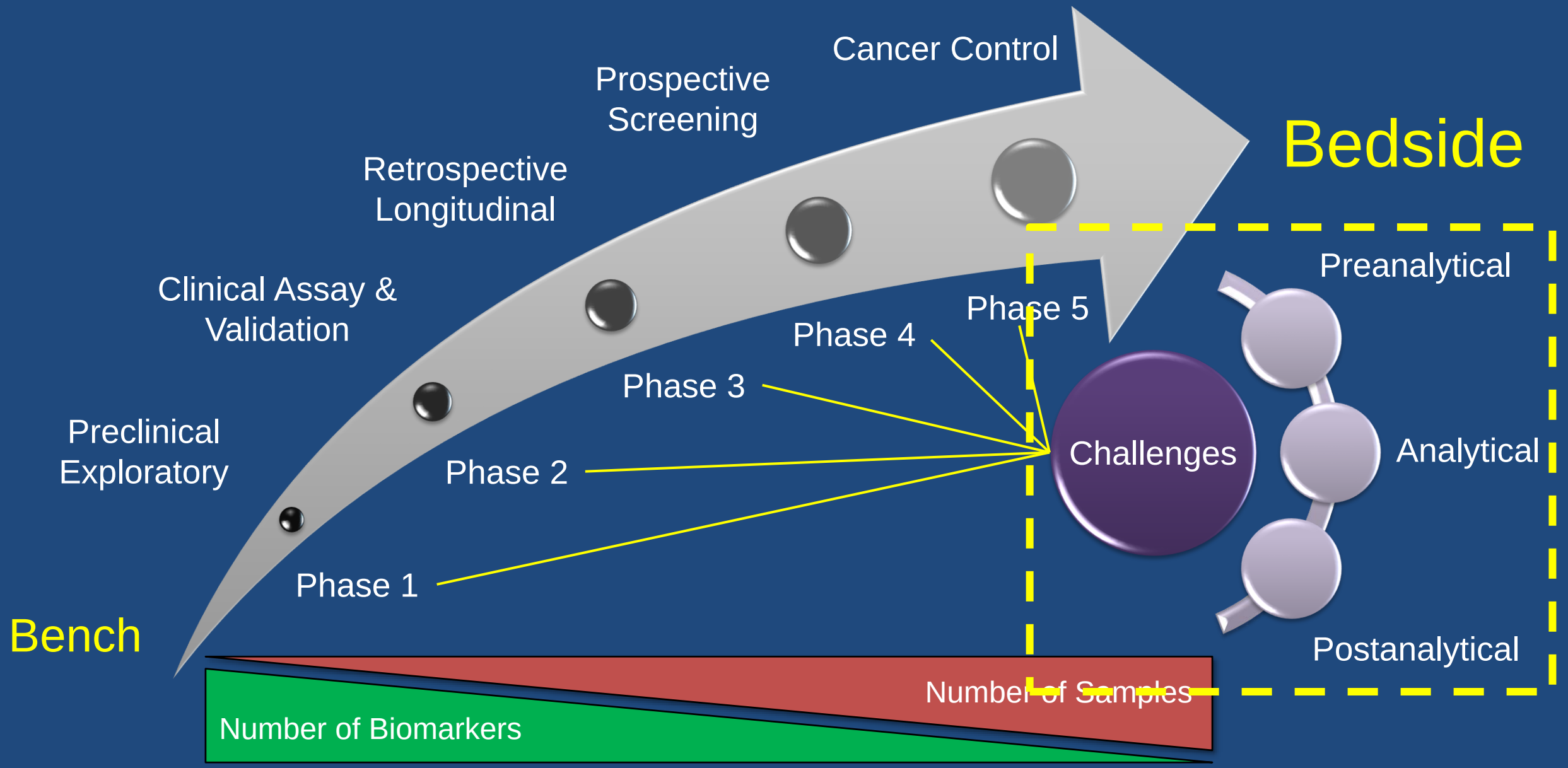
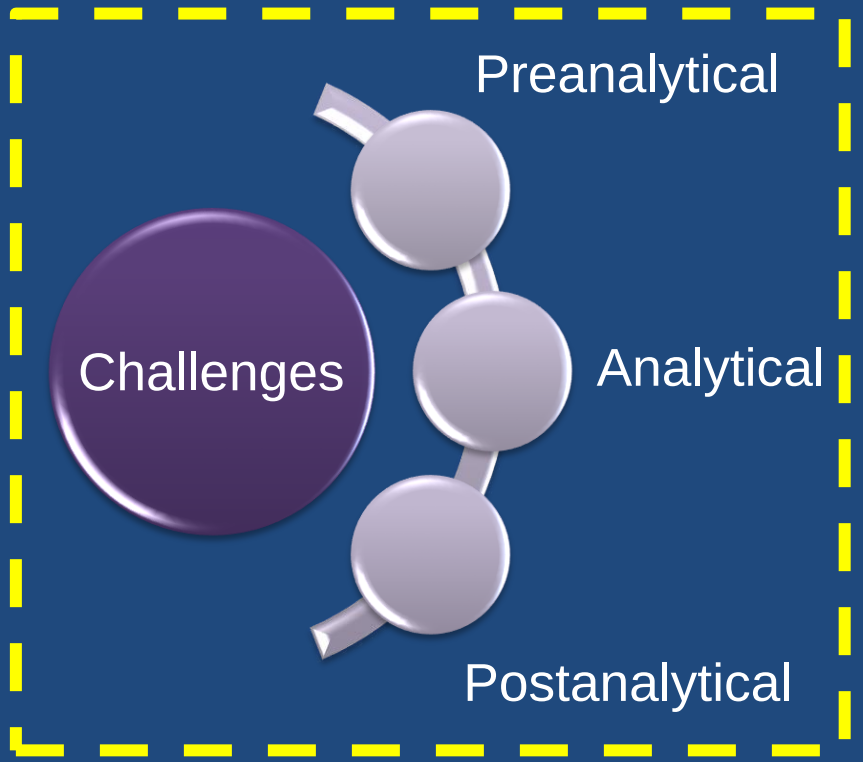
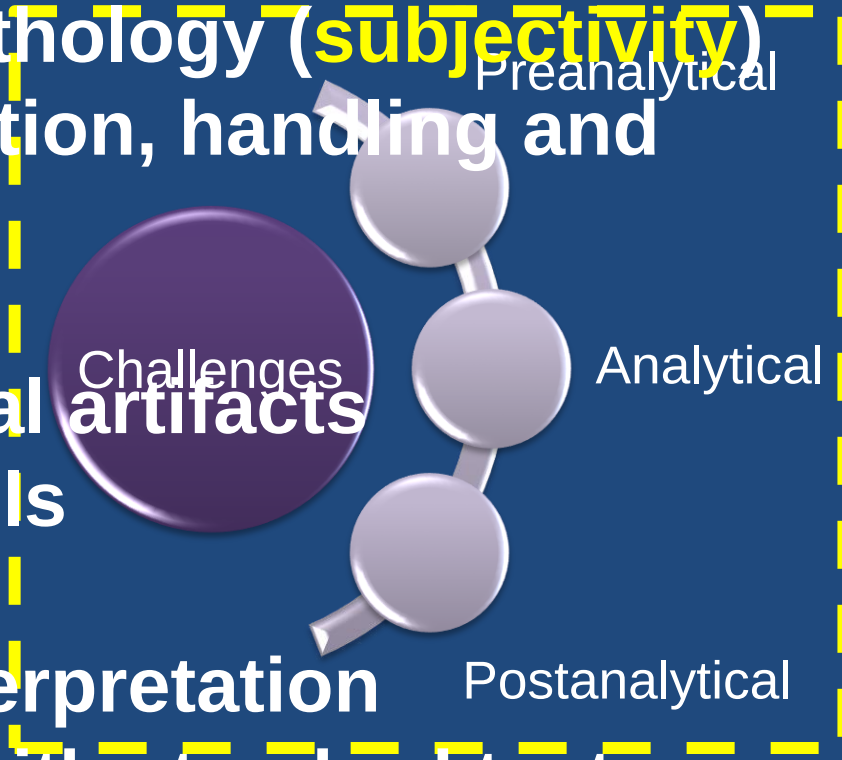


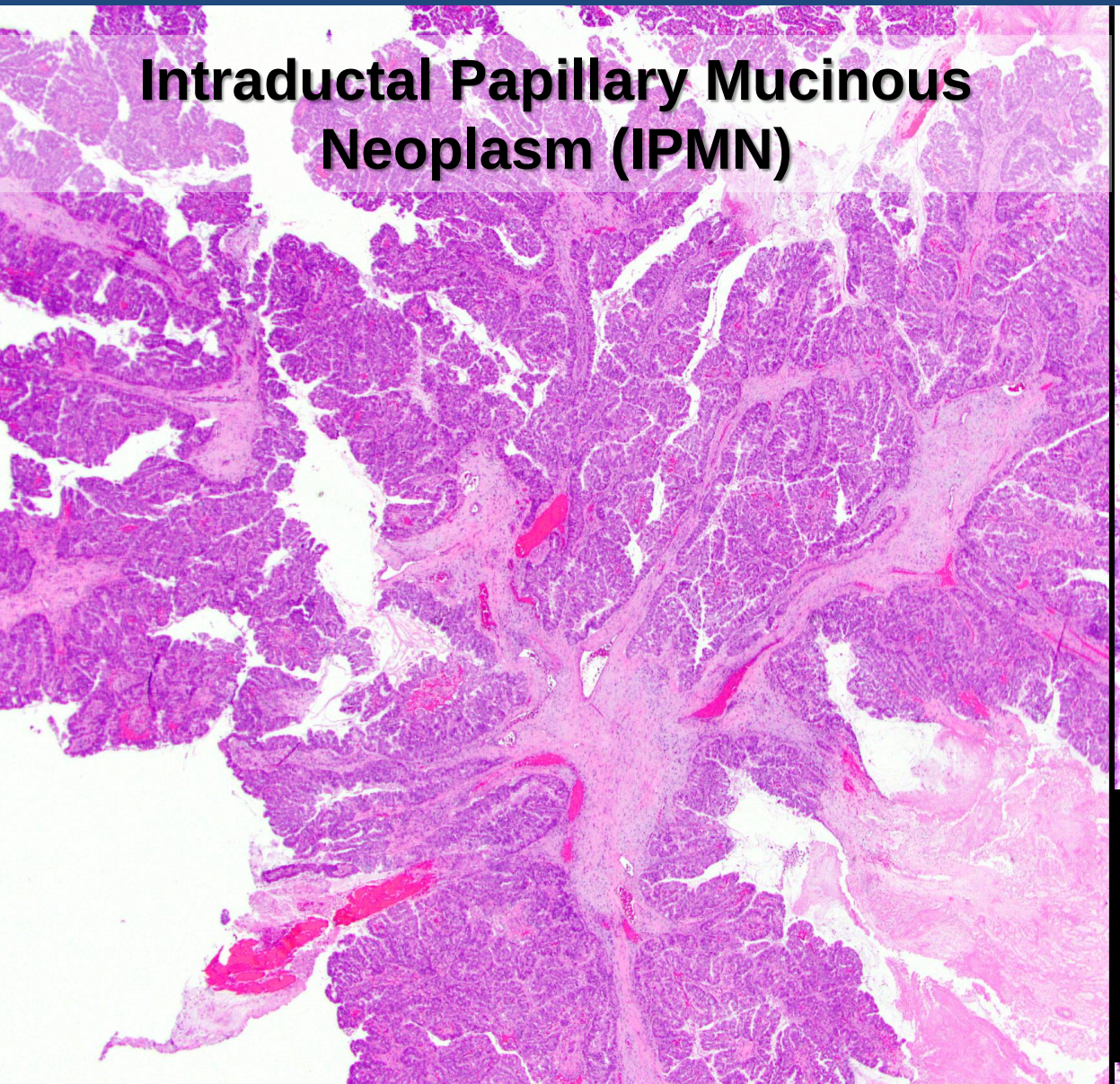
Biomarker Development

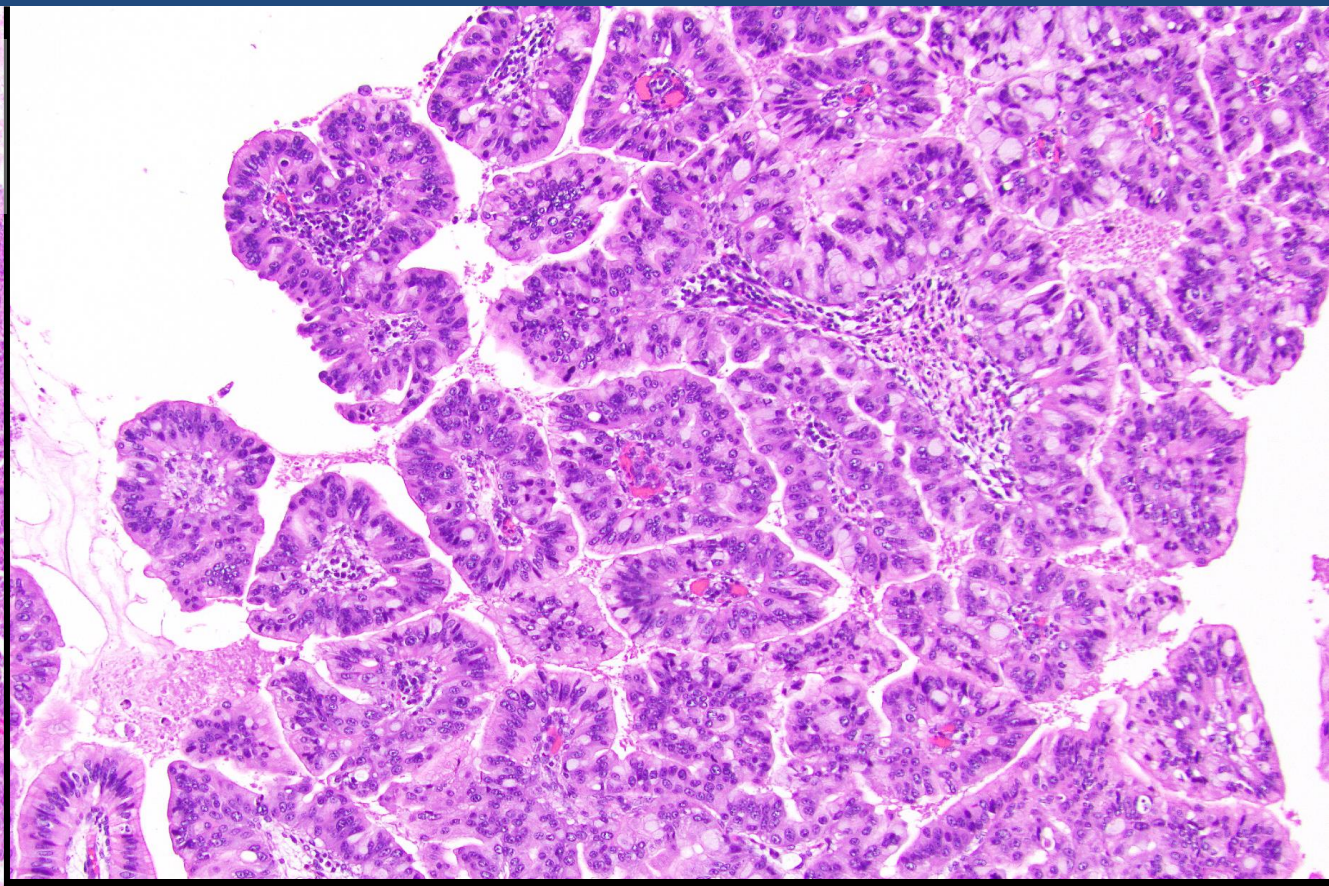


- **Preanalytical**
  - **Patient selection bias (EUS vs. surgical pancreatic cyst fluid)**
  - **Diagnostic pathology (subjectivity)**
  - **Sample collection, handling and storage**
- **Analytical**
  - **Methodological artifacts**
  - **Quality controls**
- **Postanalytical**
  - **Biomarker interpretation**
  - **Comparison with standard tests**



Pathology



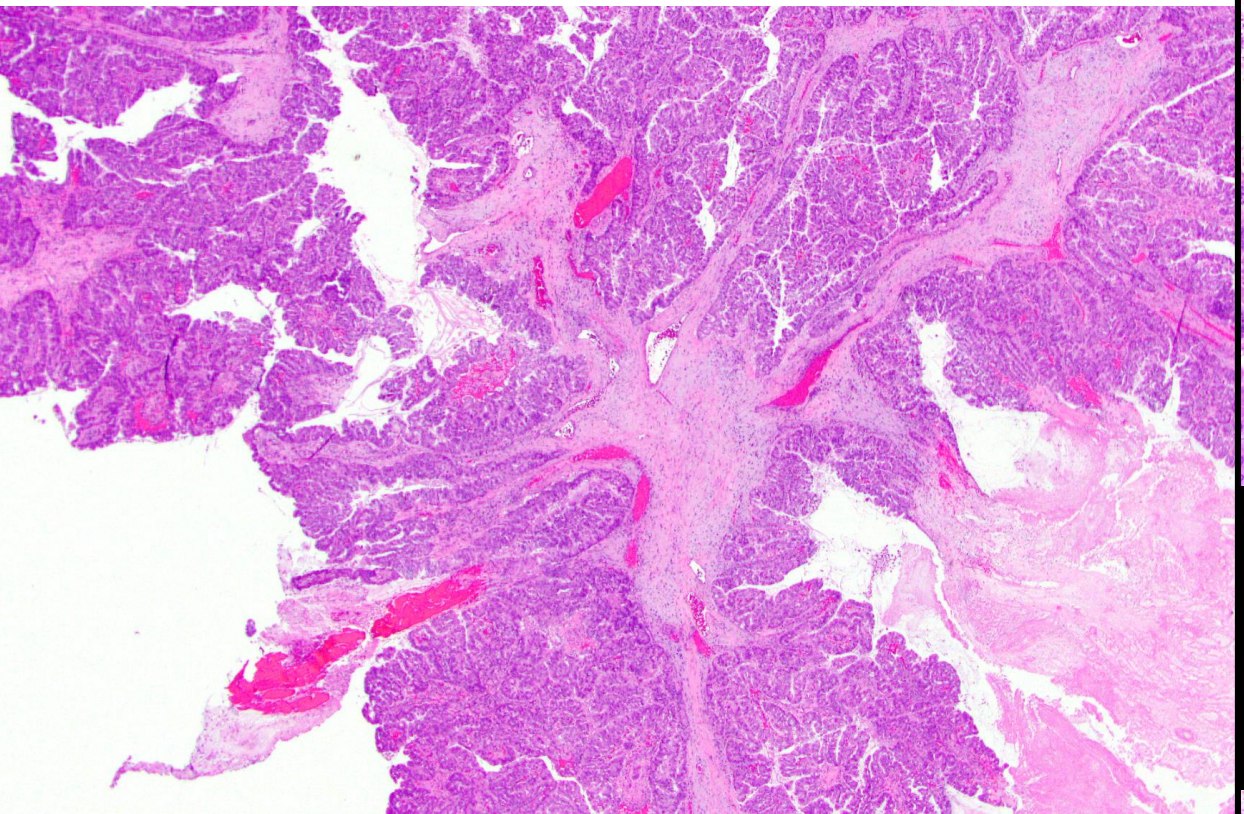


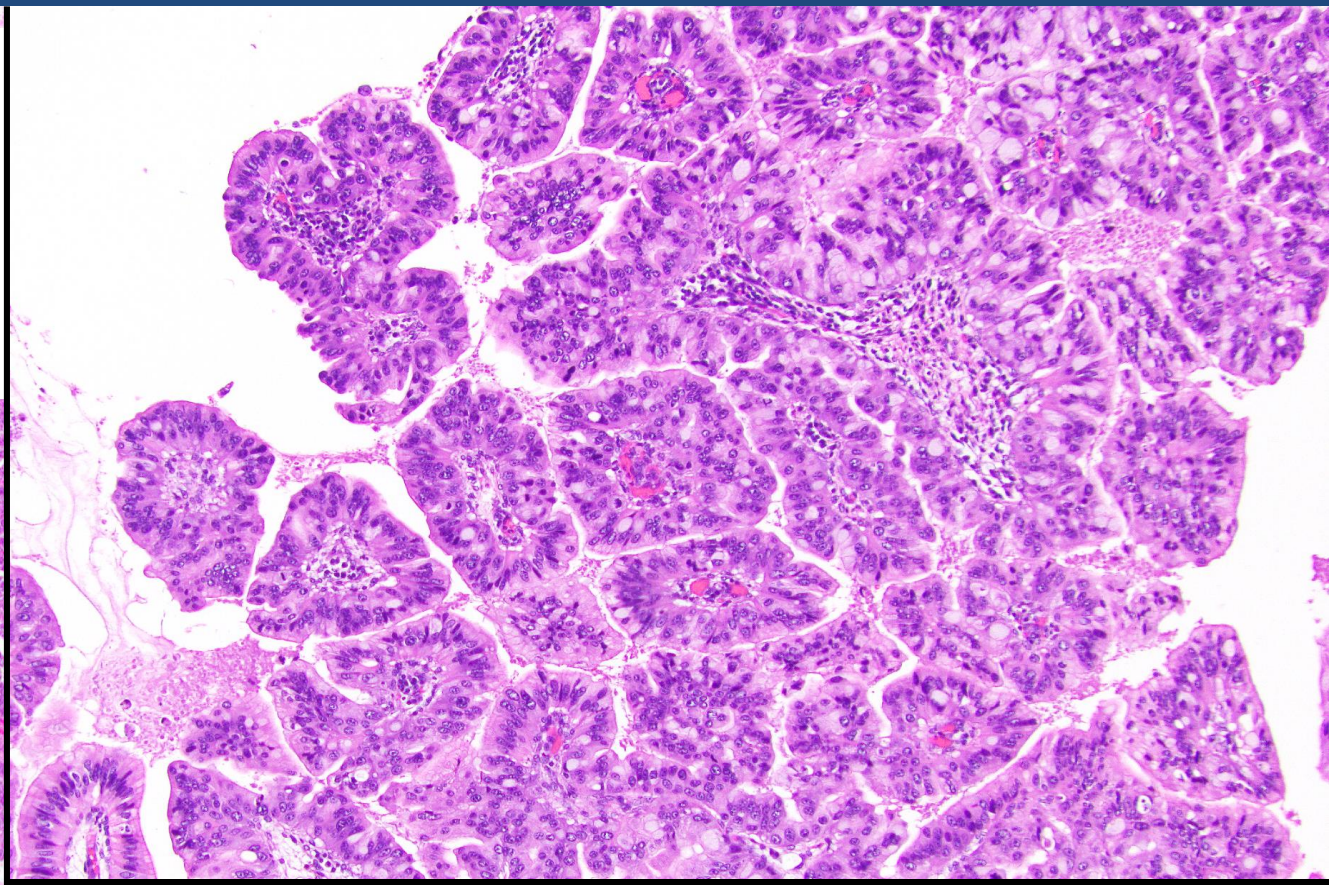
Dysplasia: High-grade or Low-grade?

Pathology

A Consensus Study of the Grading and Typing of Intraductal Papillary Mucinous Neoplasms of the Pancreas

Toru Furukawa, MD, PhD,† Noriyoshi Fukushima, MD, PhD,‡ Takao Itoi, MD, PhD,§ Nobuyuki Ohike, MD, PhD,|| Tomoko Mitsuhashi, MD, PhD,¶ Toshio Nakagohri, MD, PhD,# Kenji Notohara, MD, PhD,** Michio Shimizu, MD, PhD,†† Takuma Tajiri, MD, PhD,‡‡ Mariko Tanaka, MD, PhD,§§ Hiroshi Yamaguchi, MD, PhD,|||| Akio Yanagisawa, MD, PhD,¶¶ Masanori Sugiyama, MD, PhD,## and Kazuichi Okazaki, MD, PhD****





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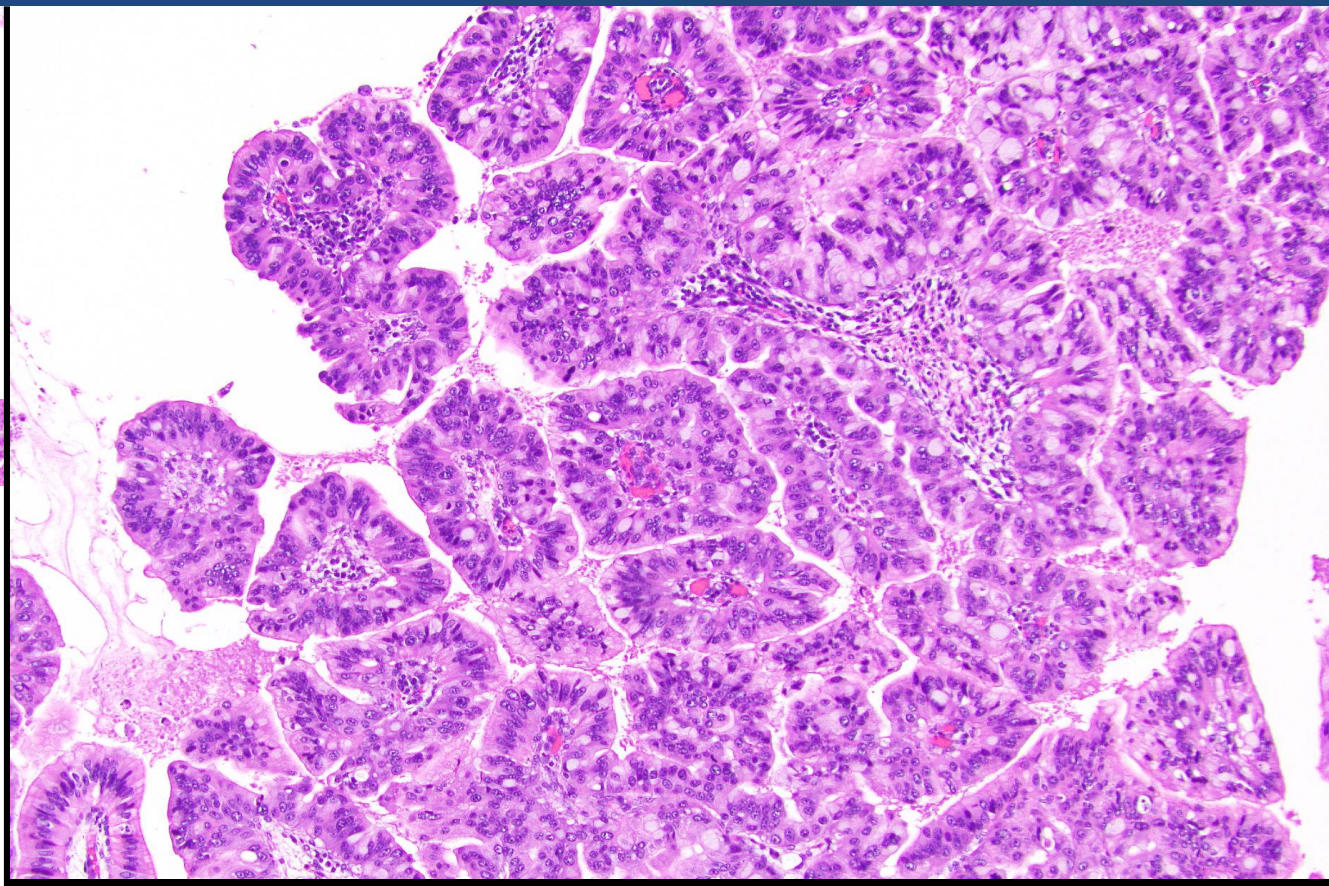
Objective: The grading and typing of intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are challenging for pathologists. We aimed to clarify the points of consistency and disagreement in assessing the grades and types of IPMNs.

Methods: Digital slide images of 20 IPMNs were independently assessed by 10 Japanese pathologists, who then held a consensus meeting to discuss the points of disagreement and develop a consensus and recommendations.

Results: The average agreement rates for grade and type were 83.5% (range, 100%–40%) and 82.5% (range, 100%–50%) and the Fleiss' κ values were 0.567 and 0.636, respectively.



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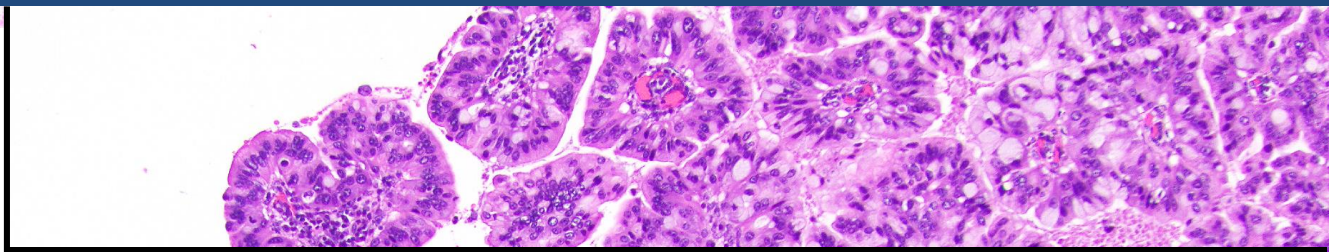
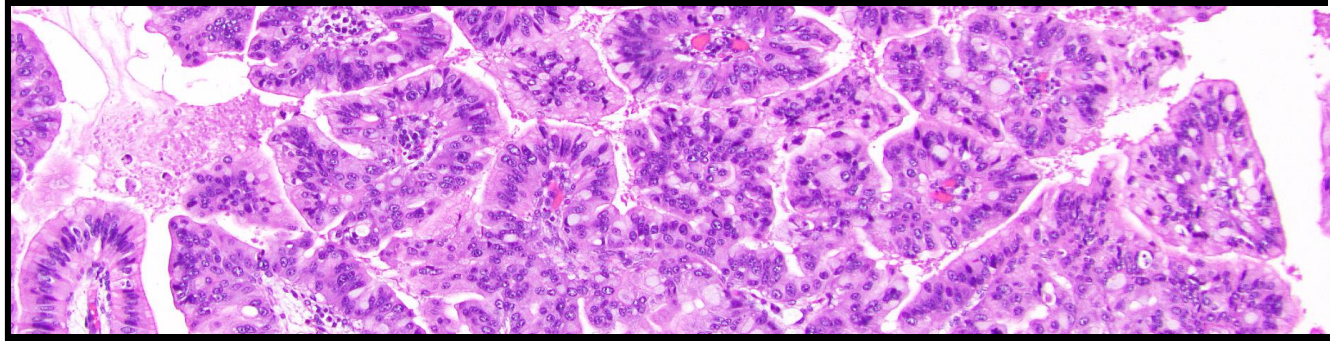


Centralized Pathology Review is Important



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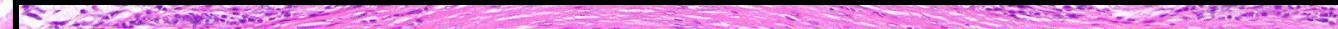
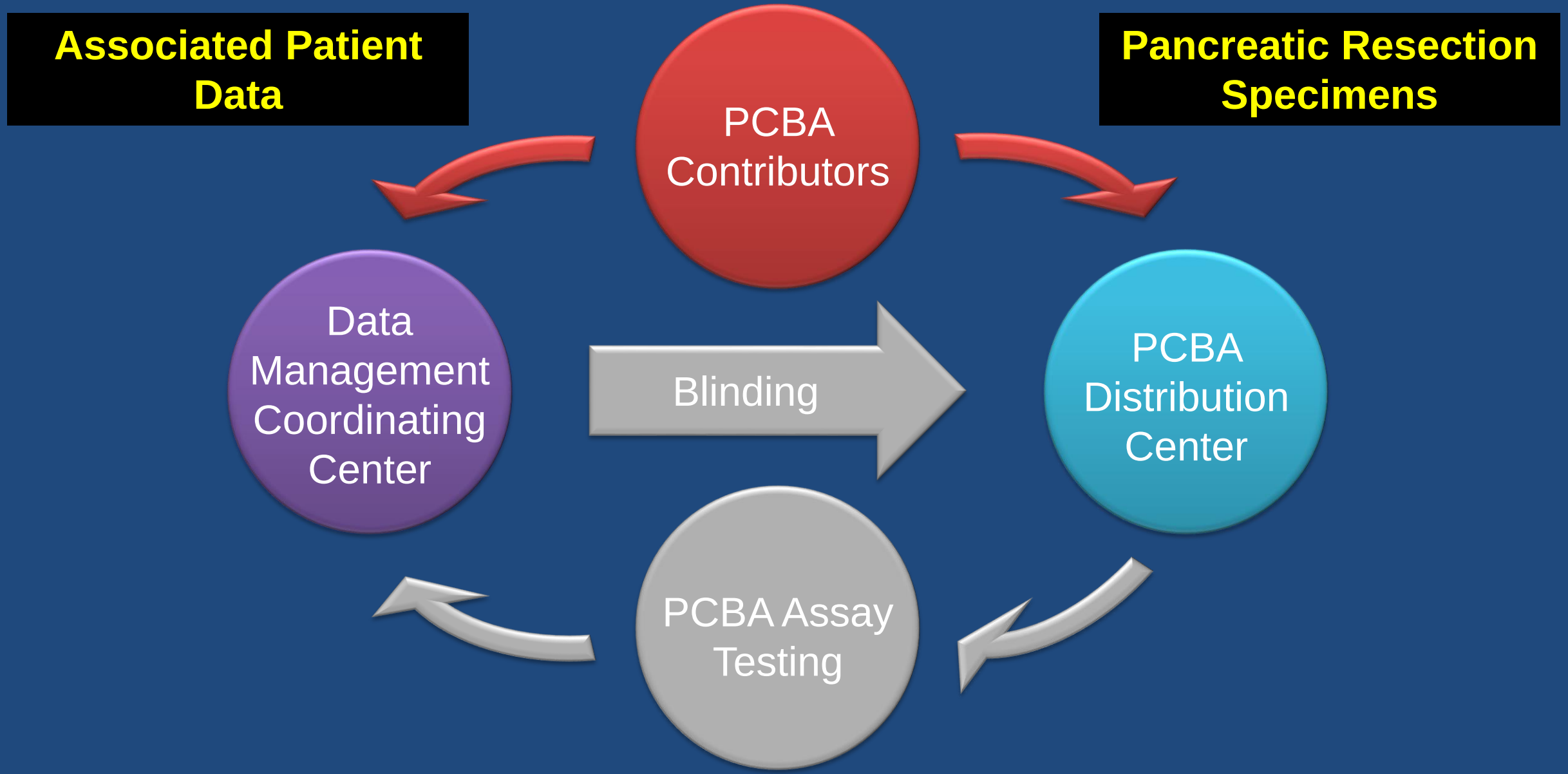


Pancreatic Cyst Biomarker Validation Study



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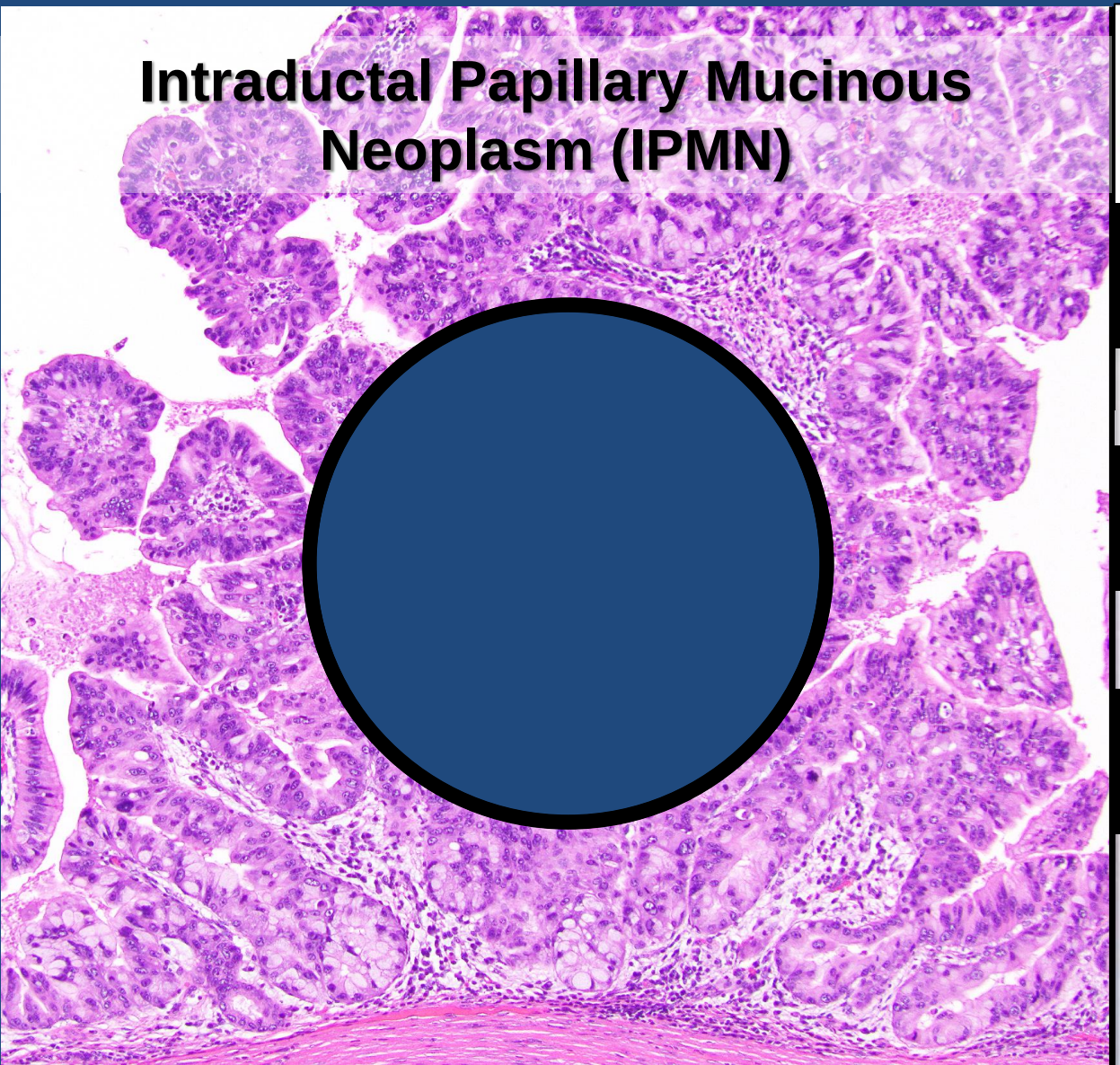
Tools for Biomarker Optimization



Digital Slide Scanning

PCBA Samples

Bake Off Samples

Separate Cohorts

Tissue Microarrays (TMAs)

- Contributing sites:
  - University of Pittsburgh Medical Center
  - University of California, San Francisco
  - Stanford University
  - Washington University
  - Johns Hopkins University

- Associated clinical and pathologic metadata (e.g. preoperative findings, CEA, etc).

PCBA Challenges

- Exploring opportunities and planning for the next phase of the **Pancreatic Cyst Biomarker Alliance.**

- Things to keep in mind:
  - **Additional investigators and assays**
  - **More specimens**
  - **Complementation of assays**
  - **Collaboration with other ongoing efforts**
  - **Reuse of specimens**
  - **Quality control mechanisms**

Pancreatic Cyst Biomarker Alliance (PCBA)

Randall Brand, MD

Charles Craik, PhD

Koushik Das, MD

Michael Goggins, MD

NATIONAL® CANCER INSTITUTE

Brian Habb, PhD

Ying Huang, PhD

Walter Park, MD

Aatur Singhi, MD PhD

Early Detection Research Network

5 minute Q&A

Chair/Co-Chair/NCI
feed Zoom Chat questions to presenter
and Track Time
NCI and Production Team
answer Chat questions not related to presentations
and use Slack